

Treatment for Advanced Prostatic Cancer

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=Abstract=Recently, there has been a proliferation of experimental and clinical data supporting early androgen deprivation for advanced prostatic cancer, due to the new insights provided by a more thorough understanding of prostate cancer biology. The long term survival of patients with prostatic metastatic disease will require the development of novel treatment strategies truly effective against anti-androgen-resistant tumor cells and their use in concert with early androgen deprivation. To date, no evidence has been generated in experimental animal or human models of prostate cancer that supports the previous concept of delayed hormonal therapy.

The development of luteinizing hormone-releasing hormone (LHRH) agonists and the anti-androgens has prompted a resurgence of interest in initial total androgen blockade, and the inhibition of the activity of 5-alpha reductase could provide a safe and effective way to remove prostatic intraepithelial dihydrotestosterone, resulting in a diminishing production of growth factors. The rationale for the use of Sumarin in the treatment of stage D prostatic cancer refractory to conventional hormonal manipulation is its ability to block the activity of several growth factors, including basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF), etc. which have been postulated to have important roles in prostatic cell biology.

Key Words: *Prostate cancer, Prostate cell biology, Endocrine treatment, Early androgen deprivation, Nonhormonal treatment*

Since the landmark observations of Huggins and Hodges in 1941, androgen deprivation has been the mainstay of treatment for advanced-stage prostate cancer. Although early, poorly controlled studies suggested enhanced survival with hormonal therapy, this view fell into disfavor as a result of the observations of the first and second Veterans Administration Cooperative Urological Research Group (VACURG) studies. Recently, there has been a proliferation of experimental

and clinical data supporting early androgen deprivation, including a reanalysis of the VACURG data, which suggests a survival advantage for younger patients with stage D disease and high-grade tumors who undergo androgen-ablative therapy at the time of diagnosis. The risk/benefit analysis presented in this review is strongly supportive of early hormonal therapy. Finally, long-term survival of patients with metastatic prostate cancer will require the development of novel treatment strategies effective against anti-androgen-resistant tumor cells and their use in concert with early androgen deprivation.

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Timing of Hormonal Therapy

Following the initial published reports of the first and second VACURG studies, the clinical pendulum appeared to shift in favor of delayed hormonal intervention (Bayer 1973; Vest and Frazier 1967). However, a number of recent studies have generated renewed interest in the concept of immediate androgen deprivation in patients with advanced-stage prostate cancer. The new insights provided by a more thorough understanding of prostate cancer biology suggested that early androgen ablation was scientifically tenable and worthy of serious reconsideration.

The VACURG survival data (Bayer and Corle 1988) concluded that younger patients with high-grade tumors (Gleason score 7-10) and stage D disease appeared to derive a survival benefit from the initiation of hormonal therapy at the time of diagnosis.

In 1985, van Aubel and associates assessed the impact of early orchiectomy on 30 patients with stage D1 prostate cancer confirmed by pelvic lymphadenectomy. Of perhaps greater significance, they noted that early orchiectomy resulted in a 46% treatment failure rate after 45 months. This interval to treatment failure compares favorably with the median interval to disease progression in patients with stage D1 disease treated with pelvic lymphadenectomy combined with radiotherapy or radical prostatectomy (15.8-36 months) and with that reported with delayed endocrine therapy (12 months) (deVere White 1983; Kramer *et al.* 1981; Prout 1980).

Because the median survival for all treatment forms in such patients is 36 months, the data suggests a longer life expectancy in patients with stage D1 disease treated by early orchiectomy. Available evidence suggests that most patients with stage D1 prostate cancer have systemic disease (van Aubel 1985; Schmidt 1983). For this reason, early orchiectomy constitutes a biologically sound form of treatment that will delay the interval to disease pro-

gression, prolong the symptom-free interval, preserve the quality of life, and permit the simultaneous initiation of other systemic measures specifically targeted to the androgen-resistant tumor component at a time when the overall tumor burden is small and thus more amenable to the cytoreductive impact of such treatment (Carter and Isaacs 1988; Isaacs 1984).

Several nonrandomized studies have suggested a benefit from early combined hormonal and cytotoxic treatment for patients with newly diagnosed stage D2 prostate cancer. Servadio and associates treated such patients with the combination of bilateral orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonist, exogenous hormonal therapy (DES or cyproterone acetate), and systemic chemotherapy (5-fluorouracil plus cyclophosphamide, 5-10mg/kg). The latter was administered weekly for 2 years, every 3 weeks for the next 2 years, and monthly for the fifth year. The authors report cumulative survival rates at 5 and 6 years of 63.5% and 50.8%, respectively. In contrast, 5-year survival rates of 25% to 40% have been reported in a similar cohort treated with hormonal therapy alone (Kramolowsky 1988; Servadio 1983; Zincke *et al.* 1986, 1987). It was suggested that the prompt initiation of multimodal systemic therapy was better tolerated and more effective when patients exhibited good performance levels and the overall tumor burden was small.

If androgen ablation is purely palliative, early hormonal therapy might prolong the symptom-free interval at the expense of inducing a shorter period where the tumor is predominantly or exclusively androgen independent and refractory to conventional therapy (Reiner *et al.* 1979). A theoretical objection to early androgen deprivation is the potentially disruptive effect of such therapy on the population dynamics or clonal stability of the tumor system. This concern implies a dynamic interaction that might include competition for nutrients and the production of inhibitory growth factors that could blunt the recruitment of dormant (resting or Go) cells into the active

phases of the cell cycle. On this basis, regression of the androgen-dependent population(s) after hormonal therapy could remove delicate growth constraints and so lead to the uncontrolled proliferation of the remaining, and potentially more aggressive cell populations. To date, no evidence has been generated in experimental animal or human models of prostate cancer that supports the concept of delayed hormonal therapy (Carter and Isaacs 1988; Isaacs 1984; Pollen 1983).

It is well established that early androgen ablation will markedly delay the onset of disease progression in the majority of treated patients. Moreover, the patient will enjoy the benefits of a longer symptom-free interval, which logically correlates with an improved quality of life (Grayhack and Kozlowski 1980; Grayhack *et al.* 1987; Vest and Frazier 1967). It is now possible to identify those patients at high risk for rapid disease progression after androgen deprivation therapy. It would appear that these patients with aggressive tumor systems are the ideal candidates for early androgen deprivation combined with other local or systemic therapies administered within the context of a controlled clinical trial. In many patients, the early detection of disease progression can be ascertained through the use of serial prostate-specific antigen determinations. Prostate-specific antigen appears to be a more sensitive tumor marker than prostatic acid phosphatase, generally increases with advancing clinical stage, is often proportional to estimated tumor volume, and may begin to rise many months before recurrence is demonstrable clinically.

The most recently recognized benefit of early hormonal therapy arose from the reanalysis of the VACURG data, which showed that younger patients with stage D disease and high-grade tumor systems (Gleason score 7-10) derive a survival benefit from such an approach (Bayer and Corle 1988).

Finally, there are a number of theoretical benefits to be derived from early hormonal therapy. Because of the impact of genetic instability,

there appears to be a trend toward increasing aneuploidy and androgen resistance as the tumor volume increases. Thus, delaying androgen ablation could promote the development of additional androgen-resistant clones, rendering subsequent therapy more problematic. Conversely, early androgen deprivation would permit the initiation of therapy in a relatively vigorous patient with a good performance level (Fordham *et al.* 1986; Frankfurt *et al.* 1985; Stamey 1982; Tavares *et al.* 1973).

To date, no truly effective treatment exists for the management of advanced-stage androgen-resistant prostate cancer. Perhaps novel approaches can be used in concert with early androgen deprivation to improve the long-term survival rate of patients with metastatic prostate cancer (Brendler 1985).

Total Androgen Blockade

Production by the testes accounts for approximately 95% of the total testosterone in circulation. The adrenal glands produce androstenedione and dehydroepiandrosterone. The LH stimulates testosterone production by the Leydig cells of the testis, whereas ACTH stimulates production of cortisol, androstenedione, and dehydroepiandrosterone by the adrenal cortex.

The concept of total androgen blockade is based on neutralization of the adrenal androgens as well as those of testicular origin. Initial attempts at total androgen blockade began in 1945, when Huggins and Scott reported the results of bilateral adrenalectomy in four patients who had failed initial endocrine manipulation. In a review by Brendler (1973), subjective improvement in prostatic cancer was shown in approximately 60% of patients, although objective remissions were rare and were not sustained. Miller and Hinman (1954) reported the results of medical adrenalectomy with cortisone. But their results were not so good. Aminoglutethimide has been used to produce medical adrenalectomy in patients with progressive prostatic carcinoma. But this drug

was removed from the market in 1966 because of the development of adrenal insufficiency in several patients.

Ketoconazole is an oral antifungal agent. At high doses, it will inhibit the cytochrome P-450-dependent enzymes in both the testes and the adrenals(Pont *et al.* 1982). Side effects, particularly gastric intolerance, limit its routine use but the drug may be useful in the patient with severe symptoms or pending spinal cord compression who cannot undergo orchiectomy.

The development of the LHRH agonists and the anti-androgens(both steroidal and nonsteroidal) prompted a resurgence of interest in initial total androgen blockade. Chronic administration of LHRH agonists will, after an initial stimulation, which peaks at 72 hours, desensitize the pituitary gland. The subsequent suppression of LH release reduces testosterone production to castrate levels(Leuprolide Study Group 1984). Leuprolide(Lupron, depot Lupron) and goserelin(Zoladex) have been approved by the US Food and Drug Administration for general use. Numerous clinical studies support the conclusion that LHRH agonists, when used as first-line treatment, are equivalent to orchiectomy or diethylstilbestrol(DES) administration. The absence of serious side effects, particularly cardiovascular, and the avoidance of orchiectomy are the primary advantages of the LHRH agonists. A flare phenomenon may occur on initiation of therapy with an LHRH agonist alone. Tumor flare corresponds to the initial stimulatory phase in which LH and testosterone levels rise and is manifested as increased bone pain or increased symptoms of bladder outlet obstruction. Spinal cord compression and increased serum creatinine concentrations can occur(Peeling 1989; Waxman 1988).

Flutamide is a synthetic nonsteroidal anti-androgen that has been approved for use in the United States in combination with LHRH analogues. Flutamide or its metabolites act to block or cause nuclear binding of androgen in target tissues(Suffrin and Coffey 1974). Side effects are rare when flutamide is used as monotherapy and generally are limited to

gynecomastia and diarrhea(Sogani and Whitmore 1984). Anandron, like flutamide, is undergoing clinical trials. Impaired dark adaptation is the most frequent side effect. Interstitial pneumonitis is rarely associated with its use(Crawford *et al.* 1989). Casodex, a pure nonsteroidal anti-androgen, is currently under clinical evaluation for the treatment of prostate cancer(Denis 1989; Freedman *et al.* 1989; Furr 1989). In 1986, at the time when clinical investigations of Casodex began, three other anti-androgens, cyproterone acetate, flutamide, and nilutamide, were available in some countries for the treatment of prostate cancer(Neumamm 1982). Flutamide effectively treats prostate cancer and appears to be better tolerated than cyproterone acetate. Because of its relatively short half-life(5.2 hours), flutamide requires administration three times daily, which can reduce patient compliance. Because flutamide is a pure anti-androgen, it acts peripherally to prevent androgen-stimulated prostate growth and centrally to antagonize the negative feedback action of androgen at the hypothalamus and pituitary gland. This antagonism results in increased secretion of luteinizing hormone(LH) and increased androgen production in the testes, as well as elevated serum estrogen concentrations. Flutamide is not associated with either cardiovascular toxicity or thromboembolism. In uncontrolled studies, the drug did not significantly suppress testicular function or libido as do progestins(Neumann 1982). The most common side effects are diarrhea, nausea, vomiting, and dizziness. Reversible liver function abnormalities have been reported in some patients. In a long-term study, 1 of 20 patients was withdrawn from flutamide therapy because of severe hepatic toxicity. When considering the pharmacologic effects of flutamide therapy, gynecomastia was noted in 61.55 of patients(Lund and Fasmussen 1988; MacFarlane and Tolley 1985). Nilutamide, another nonsteroidal pure anti-androgen, is structurally similar to flutamide. Like flutamide, it is nonselective and inhibits the negative feedback of androgens at the hypo-

thalamus and pituitary gland, resulting in increases in serum LH and testosterone. However, unlike flutamide, it has a long half-life, approximately 2 days. Clinical trials with nilutamide have focused primarily on its combination with surgical or medical castration. The side effects of the drug include problems with light-dark adaptation, interstitial pneumonitis, which regressed after drug withdrawal, and alcohol intolerance(Harnois *et al.* 1986).

A review of the properties of cyproterone acetate, flutamide, and nilutamide indicated that a nonsteroidal, peripherally selective, pure anti-androgen would have significant advantages over steroidal agents in terms of side effects and that there were opportunities to improve the efficacy, safety, and pharmacokinetics of available pure anti-androgens. Thus, the search began for a new nonsteroidal compound with a greater potency than flutamide, improved tolerance compared with flutamide and nilutamide, a long half-life compatible with once-daily oral dosing and maintenance of stable serum drug concentrations, devoid of central effects that cause increases in LH secretion and consequently of androgen production in the testes. After a search that entailed the synthesis of more than 1000 compounds, Casodex was found to satisfy these criteria best in animals(Furr *et al.* 1987). Casodex, a pure anti-androgen with a relatively long half-life, produces objective and subjective responses similar to those of surgical or pharmacologic castration and is well tolerated. Its profile makes it a strong candidate for consideration as the future anti-androgen of choice in the treatment of advanced prostate cancer.

Cyproterone acetate and megestrol acetate are synthetic steroidal anti-androgens. Both suppress LH release and interfere with the binding of androgen to the receptors. Both require accompanying small doses of DES to prevent a partial escape. Cyproterone acetate is a progestational anti-androgen with potent antigonadotropic activity that results in rapid suppression of serum testosterone. Used as

single agent, cyproterone acetate yields a total androgen blockade. It may be combined with low-dose diethylstilbestrol, orchiectomy, or LHRH agonists which improve, in theory, the results of such therapy. In clinical testing, cyproterone acetate has proved equivalent to diethylstilbestrol with markedly less toxicity. It is useful in conjunction with LHRH agonists, either transiently to block the flare phenomenon, or continuously to block peripheral androgen receptors although, the necessity for this latter action has not yet been proved. Cyproterone acetate may afford transient objective improvement in patients not responding to other forms of hormone deprivation. Experience in this role is limited. The drug may be used to suppress the hot flushes associated with orchiectomy or LHRH agonist therapy. Cyproterone acetate induces local tumor regression; owing to its reversible effects, it is useful as neoadjuvant or adjuvant androgen withdrawal therapy in patients with lower-stage disease undergoing radical surgery or radiotherapy. Adverse effects are mostly those related to hormone withdrawal, namely, impotence, infertility, and lassitude. Gynecomastia and breast tenderness occur in less than 18% and cardiovascular complications in approximately 10% of treated men. Megestrol acetate plus low-dose estrogen may be an effective, low-cost alternative to pharmacologic or surgical castration plus flutamide in the management of patients with advanced prostate cancer. The potential benefit of combined androgen blockade achieved by any means in comparison with conventional hormonal therapy appears to be limited(De Voog *et al.* 1986; Fleischmann and Catalona 1985; Goldenferg *et al.* 1988; Henry and Isaacs 1988; Pavone-Macaluso *et al.* 1986; Schroder *et al.* 1987).

In 1985, a multicenter trial was initiated in the US to test the effectiveness of total androgen blockade. Six hundred and seventeen patients were registered; 603 were eligible for treatment, of which 303 were randomly assigned to receive leuprolide 1 mg per day, and 300 were assigned to receive leuprolide 1

mg per day plus placebo. Both treatments were well tolerated. Mild diarrhea was more common during therapy but caused no significant treatment changes or discontinuation. Two hundred and sixty of the patients receiving leuprolide and placebo and 280 of the patients receiving leuprolide and flutamide were considered evaluable for response to therapy. Both median progression-free survival and overall survival were greater in the group that received total androgen blockade. The addition of flutamide lessened the flare phenomenon. Patients with minimal disease and good performance status enjoyed a more significant benefit. Neither the median progression-free survival nor the median survival time had been reached in the leuprolide plus flutamide group (Crawford *et al.* 1989).

A randomized controlled trial of leuprolide and nilutamide versus leuprolide and placebo for advanced prostatic cancer has been reported recently. The patients receiving total androgen blockade with nilutamide and leuprolide achieved a significantly higher best response rate than those receiving leuprolide alone. Fifty-three per cent of those in the combination treatment group achieved a complete or partial response compared with 41% of those receiving leuprolide monotherapy alone.

A large European study compared Zoladex with Zoladex plus flutamide in patients with either locally advanced or metastatic prostate cancer (Lungmayer 1990). Approximately 590 patients were entered from nine countries, with the end points being subjective response, objective response, and time to progression. Approximately 43% of patients entered had locally advanced (MO) disease. No difference in survival is yet apparent; however, median survivals have not been reached. As discussed, 43% of patients have locally advanced disease; therefore, one would expect the time to progression and the survival rates to be longer than in studies that include only patients with stage D2(M1) disease.

Another large study has been completed recently and reported from Denmark (Iversen

1990). This study was initiated in June 1986, and the last patient entered in December 1987. Randomization arms were either Zoladex and flutamide or orchiectomy. The end point was overall survival. Of the 262 patients entered, 172 have died, with a mean follow-up of 39 months. Some of the patients entered were in stage T3 (MO). There was no statistically significant difference in the median times to progression or survival rate in this study, but a difference was noted in objective response rates.

A similar study was carried out under the auspices of the European Organization for Research and Treatment of Cancer (EORTC) (Denis 1990). Three hundred and twenty patients were entered, and at the time of the report the median follow-up was 1.5 years. The investigators reported statistically significant increases in time to subjective and objective progression in favor of the combination treatment. No differences in time to death by cancer or overall death were recorded.

Another trial in France compared Zoladex plus flutamide with Zoladex alone for locally advanced or metastatic prostate cancer (Fourcade 1990). Two hundred and fifty patients were entered with no difference noted in survival rates. However, the median time on the study was 6 months. An Italian study compared Zoladex and flutamide in locally advanced and metastatic disease (DiSilverio 1990). Three hundred and four patients were entered, with 18-month median follow-up. There was a trend favoring Zoladex plus flutamide, as well as more normalization of prostatic acid phosphatase and bone scan and reduction in pain favoring the combination.

The majority of these studies show a slight increase in side effects in patients receiving combination therapy, and most of the studies report no significant difference in survival rate at interim analysis. With maturation of the study and combining smaller studies in a meta-analysis, the differences in progression and survival rates may emerge.

Suramin

Prostate cancer no longer responsive to conventional hormonal manipulation is associated with a poor overall survival, in the range of 9 to 18 months, regardless of the subsequent therapeutic modality employed. Further hormonal manipulation may result in symptomatic improvement in as many as 38% of patients, but objective tumor response in this setting is decidedly rare. The use of cytotoxic chemotherapeutic agents has likewise yielded only infrequent objective tumor regressions (Tannock 1985; Tannock *et al.* 1989).

Polysulfonated naphthylurea that has been used for many years as treatment for trypanosomiasis and other parasitic illness (Hosang 1985; Wills and Wormall 1950). In the early 1980s, suramin was tested for therapeutic efficacy in the treatment of AIDS after it was shown that, aside from blocking the activity of viral reverse transcriptase *in vitro*, suramin was capable of preventing both the human immunodeficiency virus (HIV) *in vitro* (Mitsuya *et al.* 1984). Unfortunately, no clinical or immunologic improvement could be documented in these studies (Broder *et al.* 1985). Most recently, a significant focus of several clinical studies of suramin has been in the treatment of stage D prostate cancer refractory to conventional hormonal manipulation (Myers *et al.* 1989). The rationale for the use of suramin in this disease is based on the following observations. Suramin is capable of blocking the activity of several growth factors, including basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF), which have been postulated to have important roles in prostate cell biology. This drug exerts an inhibitory effect on colony formation *in vitro* in two of the three commonly available human prostate cancer cells at concentrations achievable clinically without excessive toxicity. Suramin is an adrenocortolytic agent and thus may slow prostate cell proliferation through a lowering of circulating adrenal androgen levels.

Most recently, Myers *et al.* (1990) investigated the effects of suramin in patients with prostate cancer refractory to hormonal manipulation. 35 patients with metastatic prostate cancer refractory to at least one conventional hormonal manipulation have been treated with suramin and the results are available for interim analysis. Of these, eight had in addition received therapy with one or more conventional cytotoxic regimens prior to receiving suramin. Of the 15 patients with measurable disease, 3 have demonstrated complete disappearance of their sites of soft-tissue involvement with suramin therapy, and another 3 have had a greater than 50% reduction in the size of their measurable lesions for at least 1 month. However, in only 3 of these 15 patients has the overall tumor response to suramin lasted more than 3 months. With regard to bone involvement by prostate cancer, with a mean follow-up of 8 months, only 3 of 35 patients (9%) have demonstrated some improvement in bone scan abnormalities with suramin treatment, and in each case, this change became manifest only after 9 months or more of suramin therapy. An additional six patients have demonstrated areas of improvement as well as areas of worsening in their bone scans, and 11 patients have shown no change. The remainder (15) have manifested disease progress.

Serial measurements of prostate-specific antigen levels have been performed on 32 suramin-treated patients. Of these, 7 have experienced normalization of their levels. Of these seven patients, six have metastatic disease limited to bone, and only one has thus far had an unequivocal improvement in his bone scan abnormalities. Thus far, in only four of these seven patients has the duration of prostate-specific antigen normalization been longer than 3 months. Finally, of 21 patients with severe bone pain prior to the initiation of suramin therapy, 15 (71%) experienced significant relief, often in the course of the first cycle of treatment. This symptomatic improvement did not necessarily correlate with eventual objective evidence of tumor response. In addition, these

patients had been started on replacement doses of hydrocortisone at the outset of suramin therapy, and Tannock *et al.* (1989) have shown that similar amounts of steroids when used alone are capable of inducing symptomatic improvement in a significant percentage of prostate cancer patients. Thus, this improvement in bone pain may not be attributable to suramin. In each of the patients treated with suramin who eventually manifested some degree of tumor response, evidence of this nearly always appeared in the course of the first cycle of therapy, either as shrinkage of soft-tissue disease or as a significant decline in serum prostate-specific antigen levels.

A variety of toxic effects have been observed including coagulopathy, proteinuria, creatinine elevation, keratopathy, bone marrow suppression, adrenal insufficiency, and Guillain-Barre syndrome. Perhaps most prominent in this particular population have been the development of infectious complication, reversible thrombocytopenia, neuropathy, rash, and a nonspecific fatigue syndrome. This latter symptom complex, characterized by malaise, decreased appetite, and occasionally, a metallic taste, may be manifest in at least 34% of patients after completion of the first cycle of suramin infusion. It is often cumulative with successive cycles of therapy but will resolve if suramin therapy is withheld. The most serious complication is a Guillain-Barre type neuropathy (Eisen and Loveday 1973; Horn *et al.* 1988; La Rocca *et al.* 1990).

Suramin and related compounds, in view of their growth factor and enzyme binding properties, represent in many respects a novel approach to the treatment of cancer. Although in this preliminary analysis of suramin use in the treatment of metastatic prostate cancer, the objective response rate does not appear impressive, much work still needs to be done to optimize suramin's administration to patients and to elucidate its various postulated mechanisms of action. The development of related compounds with more specific enzyme and growth factor antagonist properties is

under way.

5 α -Reductase Inhibitors

The enzyme 5 α -reductase is associated with the nuclear membrane of androgen dependent target cells and requires the cofactor NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate) for the reduction of testosterone (Petrow 1986). Down regulation occurs in men after castration. Adrenalectomy and treatment with estrogens result in a mild suppression of 5 α -reductase activity. The role of DHT derived from 5 α -reductase activity in the control of luteinizing hormone (LH) and follicle-stimulation hormone (FSH) secretion from the human pituitary is difficult to determine because of the competing role of estrogens derived from the aromatization of testosterone.

Finasteride is a 4-aza steroid that competitively inhibits 5 α -reductase. This action prevents the formation of the DHT-receptor complex without affecting testosterone-receptor complex formation. Therefore, testosterone-mediated functions such as muscle mass, libido, and spermatogenesis are maintained, whereas DHT-dependent functions are suppressed. In contrast to the effects of a 5 α -reductase inhibitor, anti-androgens such as flutamide, nilutamide, and casodex block androgen-receptor binding by both testosterone and DHT, resulting in a more thorough and not less selective androgen suppression. Clinical studies in normal volunteers and men with benign prostatic hyperplasia have established that treatment with finasteride results in a significant decrease in both serum and intraprostatic concentrations of DHT (Gormley 1990). Serum testosterone levels appear to be slightly elevated whereas intraprostatic testosterone levels are substantially increased. An important observation is that both serum and intraprostatic levels of prostate-specific antigen are decreased with treatment, suggesting that the elevated testosterone levels have little or no biologic function in the prostate once 5 α -reductase is inhibited.

In men with benign prostatic hyperplasia, suppression of DHT for 6 months results in a 28% reduction in prostatic volume(Gormley 1991).

These studies have established that, at least in the benign prostate, DHT is the obligate androgen. Whether malignant prostate tissue retains this selectivity remains to be determined.

If prostate cancer cells are dependent on DHT and not testosterone for neoplastic growth, 5 α -reductase inhibitor could provide a safe and effective way to remove DHT selectivity. This approach would have the unique advantage of suppressing the growth of the carcinoma without interfering with important testosterone-dependent functions such as the maintenance of bone mass, muscle bulk, sexual function, and libido. This selective effect would be highly desirable to many patients if the clinical efficacy were equivalent to or better than that of nonselective treatments. Clinical trials with finasteride are under way to evaluate this option.

There is some evidence that combined anti-androgen therapy using two drugs with different mechanisms of action provides better results than single-agent therapy alone. The goal of combination therapy is to block both testicular and adrenal sources of androgens. The adrenal cortex secretes significant amounts of androstenedione, dehydroepiandrosterone, and DHEA sulfate, which can be converted to DHT and concentrated within the prostate (Geller *et al.* 1988; Lyss 1987). In studies correlating intraprostatic DHT levels and protein synthesis, very low levels of DHT have been found to regulate intraprostatic protein synthesis. The importance of adrenal androgens in the pathogenesis of prostate cancer is also suggested by several studies demonstrating a clinical response to anti-androgen therapy in patients who have relapsed after orchiectomy. Additional evidence comes from several clinical trials showing that the combination of an LHRH analogue and flutamide is more effective than LHRH alone(Crawford *et al.* 1989). The combination of a 5 α -reductase inhibitor and an LHRH analogue could provide an effective means of

blocking adrenal sources of DHT. Because the combination would not preserve plasma testosterone levels, the selective advantages of 5 α -reductase inhibitors would be lost.

The incidence of clinically recognizable prostate cancer, combined with the large percentage of men observed to have occult prostate cancer, combined with the large pre-pubertally castrated males and men with androgen-insensitivity syndrome. This has led to the hypothesis that lifelong exposure to androgens is a risk factor for the development of prostate cancer. If this is true, then suppression of DHT with a 5 α -reductase inhibitor prior to the development of clinically recognizable disease may have a protective effect, resulting in a decreased incidence of prostate cancer.

The rise in circulating and intraprostatic testosterone concentrations in men treated with a 5 α -reductase inhibitor could be offset by the rise in testosterone. Because intraprostatic prostate-specific antigen levels and prostate volumes decrease in men with benign prostatic hyperplasia treated with finasteride, this does not appear to be a significant problem. Whether prostate cancer cells respond in a similar way remains to be shown.

Future Direction of Study for Nonhormonal Systemic Therapy

Hormonal ablation has remained the standard therapy for metastatic prostate cancer. More than 80% of men will respond initially to hormonal intervention, suggesting that a portion of their tumor cell population is androgen responsive. However, given time, the majority of these men will relapse to a hormonally unresponsive state for which we have no effective therapy at present. Treatment by androgen withdrawal would be expected to impact only on androgen-dependent or androgen-sensitive cells.

One approach to eliminating the non-androgen-dependent tumor cells would be the use of cytotoxic chemotherapy. Differing re-

sponse rates have been reported for the same agents, leading to confusion regarding this form of nonhormonal therapy. When patients were categorized into risk groups according to their symptoms and signs, patients with poor performance status and extensive disease had a worse prognosis. It thus appeared that survival was a function of the natural history of the tumor rather than the type of therapy administered. The interpretation of response rates has been obscured further by including patients with stable disease as responders; although these patients survive longer than those with progressive disease, this survival benefit cannot be ascribed solely to chemotherapy (Warner and Heston 1991).

The limitations related to the nonspecific nature of conventional cytotoxic chemotherapy have provided the impetus for the development of new approaches in this form of non-hormonal management of prostate cancer. Bagshawe (1988) reviewed a novel approach for the increased delivery of cytotoxic therapy to tumor sites. The principle of targeting of systemic agents is intended to maximize the product of drug concentration and time in the target cells. This system is based on tumor cell characteristics that allow it to be identified as distinct from normal; a growth factor, protein, or polypeptide, for example. Most work recently has been based on tumor- or tissue-specific antigens.

Although cytotoxic therapy has been the mainstay in the treatment of hormonally resistant prostate tumor, its impact on survival has remained relatively small. New agents that kill nondividing cells and novel methods of administration will be required in order to make a significant contribution to the nonhormonal management of prostate cancer.

Stromal-epithelial interactions

In a recent work by Chang and Chung (1989), the interaction of normal prostatic fibroblasts and epithelial cells and the role of androgens were investigated using coculture techniques. They demonstrated that although

the primary site of conversion of testosterone to dihydrotestosterone (DHT) is the prostatic epithelial cell, the primary target for DHT-elicited mitogenic action is the prostatic fibroblasts. They suggested that intraepithelial DHT may stimulate the production of growth factors that act on the producing cells (autocrine) or on fibroblasts (paracrine), whereas DHT released into the extracellular pool acts primarily to stimulate the prostatic fibroblasts.

The most frequent clinically recognized site of dissemination in human prostate cancer is the bone. Chakal-Roy *et al.* (1989) proposed that the marrow, acting through selective cell-cell interactions and growth factor release, provides a privileged environment for prostate cell growth. Recently, Finch *et al.* (1989) characterized a growth factor similar to fibroblast growth factor (FGF) that is produced by human embryonic lung fibroblasts. This keratinocyte growth factor (KGF) has demonstrated mitogenic activity limited to epithelial cells without action on the producing fibroblasts. This observation contributes further support to the stromal-epithelial interaction hypothesis. The ability to manipulate stromal-epithelial interaction in the future management of prostate cancer will require a greater appreciation of the intercellular dependence and knowledge of the growth stimulating factors responsible for the transformation of the primary tumor and the formation of metastases.

Growth factors

A number of growth factors have been identified in normal, hyperplastic, and malignant prostate tissue that appear to work by autocrine or paracrine mechanisms. Of the stimulating polypeptides, FGF, epidermal growth factor (EGF), and transforming growth factor alpha (TGF α) have been the most widely studied, with FGF being a significant growth factor in rat and human prostate tissue (Warner and Heston 1991).

FGF is a member of the heparin-binding growth factor family (HBGF), which includes the gene product of HBGF-1 (acidic FGF) and

HBGF-2(basic FGF), as well as the int-2 gene product, the hst gene product(Kaposi sarcoma FGF), FGF-5, FGF-6, and KGF. The HBGF family members have a wide range of actions. They are potent mitogens for both prostate epithelial and mesenchymal cells(McKeehan *et al.* 1984), and are involved in autocrine stimulation of cells as well as paracrine neovascularization and osteoblastic activity of prostate tumors. In human tissue, content of HBGF increases in benign and malignant prostates(Nishi *et al.* 1988). In patients undergoing radical prostatectomy, the mean total growth factor content per gram of prostate is significantly lower in patients receiving estrogen therapy prior to surgery than in untreated patients, suggesting that only a portion of the growth factor content is hormonally dependent. Although implicated, the heparin-binding growth factors have not been proved to be involved directly in the etiology of prostatic neoplasms.

Epidermal growth factor is a potent mitogen for a wide variety of cells, yet its role in the prostate is unclear. This factor and its receptor have been identified in human prostate and in rat ventral prostatic tissue(Jacob and Story 1988). Traish and Woltz(1987) demonstrated the downregulation of EGF receptors in the prostate by androgens and proposed that androgen deprivation might allow EGF receptor induction and so promote cell growth, thus preventing complete prostate regression after castration. The change in cellular composition of the androgen-treated prostate and its possible impact on growth factor binding were not addressed.

Transforming growth factor alpha binds to the EGF receptor and is considered to be the embryonic form of EGF because of its presence in a large number of normal fetal tissues. It has been implicated as an autocrine stimulatory growth factor in a variety of tumor cell systems, including breast, kidney, and colon. This may represent an important growth control mechanism in the prostate, as human cell lines produce, secrete, and respond to TGF α (Connolly and Rose 1988; Derynck *et al.* 1987; Dickson

and Lippman 1987).

Cell growth is the result of both stimulatory and inhibitory signals. Transforming growth factor beta inhibits the growth of normal rat prostate epithelial cells but stimulates the growth of prostatic fibroblasts synergistically with FGF. TGF beta receptor in normal rat ventral prostate is under negative androgenic regulation, indicating a possible role for this growth factor in the castration-induced death of hormone-sensitive cells(Kyprianou and Isaacs 1988; Shain *et al.* 1990).

Tumor necrosis factor(TNF), also called cachectin because of its proposed action of protein wasting in chronic infection and cancer, is cytotoxic to the human prostate cancer cell lines but not to benign prostatic epithelial or stromal cells. Its potential role in the management of hormone-resistant prostate cancer remains to be defined(Sherwood *et al.* 1990).

Thus, normal and abnormal cell growth is regulated by peptide growth signals, which provide a framework for the design of therapeutic intervention. Interruption of the effector polypeptide-receptor interaction could be accomplished by blocking the growth factor at its active site, or by an extracellular antagonist that would compete for receptor site. In hormone-refractory prostate cancer, it remains unclear exactly which growth factors are important.

Oncogenes

The Dunning R3327 rat prostate adenocarcinoma system demonstrates many of the characteristics of tumor progression seen in human prostate cancers and has served as an excellent animal model to investigate prostate cancer. Viola *et al.* (1986) used an immunohistochemical assay to assess expression of both the unaltered and the mutated ras protein p21 in normal and neoplastic tissue. Epithelial and stromal cells from patients with normal prostate or benign prostatic hyperplasia were negative for the p21 antigen, but two of the six grade 1 lesions, four of the six grade 2 tumors, and all 17 of the higher-grade cancers showed

p21 expression, However, Varma *et al.*(1986) found no consistent difference in p21 expression between benign and malignant epithelium, and no correlation between grade and staining intensity could be demonstrated. Buttyan *et al.* (1987) used surgical specimens of benign and malignant human prostate tissue and found no increase in c-Ha-ras transcripts in malignant tissue by northern hybridization. Carter *et al.* (1990) and Poonamallee *et al.* (1990) have found ras gene mutations to be uncommon in prostate cancer. These results call into question a role for ras mutations in prostate cancer; however, their role in hormonally resistant tumors remains to be investigated.

Evidence is accumulating for the presence of a second group of genes that counteract the expression of the tumorigenic phenotype. Suppression of tumorigenicity in hybrids of normal and malignant cells and the regular loss of both alleles of a single gene in cancers such as retinoblastoma or Wilms' tumor has suggested the presence of these tumor suppressor genes. Huang *et al.* (1988) introduced, via retroviral-mediated gene transfer, a cloned RB gene into retinoblastoma and osteosarcoma cells that had inactivated endogenous RB genes. marked suppression of the neoplastic phenotype and complete loss of tumorigenicity in nude mice was recorded. Bookstein *et al.* (1990) examined three human prostate lines, DU-145, LNCaP, and PC-3 for RB expression. The DU-145 cells contained an abnormally small protein translated from an RB mRNA transcript that lacked 105 nucleotides encoded by exon 21. Normal RB expression was restored by retroviral-mediated transfer of the normal gene into the DU-145 cells. This insertion of the normal gene led to loss of tumorigenicity in nude mice despite unaltered cellular growth curves in vitro.

The possibility of a third group of genes that modify the behavior of malignancies through controlling cellular resistance to immune rejection or invasiveness by controlling proteolytic and homing mechanisms has been proposed. The application of this form of ther-

apy requires the identification of specific molecular lesions associated with prostate cancer. However, genetic engineering has allowed the insertion of antitumor activity into the cell without this identification(Fenyo and Klein 1988).

Tumor-infiltrating lymphocytes inhibit the Dunning rat prostate tumor cells and human prostate tumor cells alone and in combination with interleukin(IL)-2 and cyclophosphamide. The development of cells with secretory capacity for IL-2, TNF, and other factors would allow the production of a more sustained immune response without the regulation by the host suppressor systems(Warner and Heston 1991).

Agents also are being developed that modulate the basic cellular mechanisms responsible for the emergence and persistence of cancer. Wenger *et al.* (1985) demonstrated that treatment of prostate tumor-derived MAT-Ly-Lu cells with 2.25% DMSO decreases the growth rate, saturation density, and clonogenicity; increases the doubling time; and alters enzyme activity and tumorigenicity.

The receptor for retinoic acid has been well characterized. It is a member of the steroid and thyroid hormone-receptor superfamily, and is present in rodent and human prostate cancer tissue, increasing with androgen blockade, Wouters *et al.* (1990) reported pronounced antitumoral activity in the Dunning R3327G rat prostatic tumor model and in hormonally insensitive stage D prostate cancer patients by the imidazole compound R75-251. Although its mechanism of action is unknown, this compound increases serum retinoic acid levels by inhibiting vitamin A degradation.

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